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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,995	KIVITS ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *8-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/8/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

Applicant's election, with traverse, of the Group I, claims 1-7, drawn to a process for extracting transforming growth factor β (TGF-β) from a milk product, filed on 17 April 2006 in response to the 17 March 2006 office action is acknowledged. The traversal is on the following ground(s):

1. The extraction process steps together lead to the separation of a first fraction rich in TGF-β and a second fraction rich in IGF-1, and thus the separation technique of isolating fractions of TGF-β and IGF-1 represent a single Invention

2. Groups III and IV are linked to Groups I and II as they share the special technical feature of a separation method with Groups I and II

3. The International Examiner, examining the same claims in the PCT application, found no lack of unity.

Applicants assert that "a proper lack of unity determination would require a citation of a reference showing the 'special technical feature'" (page 2 of Remarks of 17 April 2006).

Applicants' arguments have been fully considered, and have been found persuasive in part. Upon further consideration, the restriction between Groups I and II is removed, and Group II is rejoined with Group I. The restriction between these two groups and Groups III and IV remains. Groups I and II are drawn to methods. Groups III and IV are drawn to protein products. These Inventions are separate and distinct and require separate searches of the Art.

Furthermore, Application 10/089995 is being examined under US regulations and practices, not by the International Search Committee. The PCT examination is not binding on U.S. national prosecution. The expression "special technical feature" is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions considered as a whole, makes over the prior art (See MPEP 1850, Section II). The rule does not require a citation of a reference showing the

"special technical feature". Applicants have failed to identify a common disclosed structural feature between Groups I and II (method) and Groups III and IV (products) which would support the assertion that the two groups are similar in scope.

The requirement is still deemed proper and is therefore made FINAL. in the instant application. Claims 8-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-7 are under examination.

Objections

Information Disclosure:

References submitted on IDS filed 8 April 2002 are not in compliance with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 for the following reasons: Reference JP 00279312 has not been included with the instant application. Therefore this reference has been lined through and has not been considered.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claims:

Claim(s) 1-7 are objected to because of the following informalities: The claims start by reciting "Process .....". The appropriate article should precede the word "Process". Appropriate correction is required.

Claim 2 is objected to because of the following informalities: it contains a typographical error: hydroyapatite should read as hydroxyapatite. Appropriate correction is required.

Claim Rejections

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, the independent claim of the instant invention, is an incomplete method claim. To be complete, a method claim must state a goal in the preamble of the claim, and conclude having achieved that goal. The Claims are also incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps include a recitation of the starting material, a clear sequential statement of the two elution steps, and a conclusionary statement. Step 1a is a statement of a goal i.e. "recovering a basic fraction". It does not clearly indicate how this is to be accomplished. Step 1c recites "increasing salt concentration or pH....". It is unclear whether applicants intend the eluent to have increasing pH values. Step 1c further recites step c)i) "wherein the ratio IGF-1 to TGF-β is greater than 10" and; step c)ii) "wherein the ratio TGF-β to IGF-1 is greater than 5". The term "ratio" is generally taken to mean the relationship in quantity, amount or size between two or more things, or a proportion. It

is unclear if applicants intend "the ratio of IGF-1 to TGF-β is greater than 10 to 1" and "the ratio of TGF-β to IGF-1 is greater than 5 to 1"

Claim 2 recites step d) eluting the hydroxyapatite column with an eluent having increased salt content or pH as compared to the eluent used in step c). It is unclear if applicants intend this step to be undertaken after step c in claim 1. Additionally, it is unclear whether applicants intend the eluent to have increasing pH values. Furthermore, the claim recites "said eluent". It is unclear to which eluent the term "said" refers: the eluent of step d) or the eluent of step c.

Claim 5 recites "wherein step a) is carried out by passing the milk product at high surface velocity and a high liquid load". These terms are relative terms and are not defined in the specification. Rather, exemplary conditions are taught in the specification. Thus, is unclear what conditions applicants intend as their invention.

Claims 3, 4, 6 and 7 are included in this rejection since they depend from rejected claims.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for extracting TGF-β and IGF-1 and lactoperoxidase from a milk product comprising the steps of:

a. eluting a basic fraction (from the milk product adsorbed unto cation exchange column) by eluting components from cation exchange with a 0.24M NaCl solution, pH 5.5-7.5 or a 0.28 M NaCl/10mM ammoniumacetate solution, pH 5.5

b. passing the basic fraction (from step a) over a hydroxyapatite column

c. eluting the hydroxyapatite column sequentially with phosphate buffers of increasing salt concentrations and increasing pH or eluting the hydroxyapatite column with a buffer containing increasing concentrations of NaCl/phosphate

thereby eluting, sequentially, fractions enriched for IGF-1, TGF-β, and lactoperoxidase

does not reasonably provide enablement for

for a process for extracting TGF-β and IGF-1 and lactoperoxidase from a milk product comprising the steps of:

a. eluting a basic fraction from a cation exchange column by utilizing any elution buffer

b. passing the basic fraction (from step a) over a hydroxyapatite column

c. eluting the hydroxyapatite column sequentially with increasing salt concentrations or increasing pH concentrations, said eluents being any phosphate buffers, sodium chloride solutions and potassium chloride solutions

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are broadly drawn to a method of isolating two or three specific growth factors, IGF-1, TGF-β, and lactoperoxidase, from milk product by a two step process. The process comprises using first cationic exchange chromatography to isolate a fraction containing all three growth factors, and then passing this basic fraction over a hydroxyapatite column and sequentially eluting fractions rich in IGF-1, rich in TGF-β, and rich in lactoperoxidase.

The specification teaches that after the adsorption of the desired components onto the cationic exchange resin, an elution step is carried out. The preferred elution solution is one comprising sodium chloride or potassium chloride buffered at pH 5.5 and 7.5. This results in a fraction containing the desired TGF-β, IGF-1 and lactoperoxidase (page 16, lines 25-29). The working examples (Example 1, page 20, lines 24-23; Example 2, page 21, lines 16-22; Example 3, page 22, lines 5-12) teach elution of growth factor rich fractions with buffers of 0.24 M NaCl, pH 6.5 (example 1 and 2) or 0.28 NaCl/10 mM ammoniumacetate, pH 5.5. The art teaches purification of polypeptide growth factors from milk by eluting the fraction rich in growth factors off of a cation exchange column utilizing buffers of 0.6M NaCl (1987. Shing et al. Methods in Enzymology. 146:42-48, page 46, 1st paragraph), 0.5M NaCl (1997, Belford et al. J of Endocrinology 154:45-55, page 47, column 1, 1st paragraph, cited on IDS of 8 April 2002) and 0.2-1.0M NaCl (1998. Kussendrager et al. EP 0869134, column 6, lines 43-51, cited on IDS of 8 April 2002). Thus, both the specification and art teach isolation of a fraction from milk products enriched for growth factors by elution from a cation exchange column utilizing a buffer with a high NaCl concentration.

The specification teaches a second step in the purification process comprising passing the fraction obtained by the first step over a hydroxyapatite column. After the adsorption step, the hydroxyapatite column is eluted sequentially with suitable eluting liquids. The disclosure then asserts that "to obtain an IGF-1 enriched fraction the column is ...eluted with a phosphate buffer having a pH of 5.5-7 and a phosphate concentration of 0.05-0.2M.....To obtain a TGF-β enriched fraction the column is subsequently eluted with a phosphate buffer having a pH of 5.5-7 and a concentration of 0.2 to 0.3M" (page 17, lines 19-24). "A further elution step is carried out to recover a lactoperoxidase fraction.....with a phosphate buffer having a pH of 5.5-8 and a phosphate concentration of 0.3 to 0.5M" (page 17, lines 29-32). The art teaches that a buffer comprising phosphate concentration of 0.1-0.5M concentration is utilitzed to elute a fraction rich in growth factors (from starting material of skimmed colostrum) off a hydroxyapatite column (1992, Quinque et al. WO 92/00014, cited on IDS of 8 April 2002).

Thus, the specification and the art teach elution conditions comprising steps using specific elution buffers in order to obtain fractions enriched with IGF-1, or enriched with TGF-β or enriched with lactoperoxidase, limitations recited in claims 1 and 2. The skilled artisan would have to undertake undue experimentation to determine which buffers at which concentrations and pH to utilize in first step and which phosphate, NaCl or KCl buffers at which concentrations and pH to utilize in the second step in order to achieve the goal of obtaining a fraction comprising IGF-1, wherein the ratio IGF-1 to TGF-β is greater than 10; a fraction comprising TGF-β, wherein the ratio TGF-β to IGF-1 is greater than 5; and a fraction comprising lactoperoxidase, as required by limitations recited in Claims 1 and 2.

Due to the large quantity of experimentation necessary to determine the types of elution buffers, including concentration and pH, to use to obtain the fractions recited in the claims, the lack of direction/guidance presented in the specification and the absence of working examples directed to chromatography conditions other than those specifically listed above, the complex nature of the invention, the state of the art that teaches isolation of growth factors using cationic exchange chromatography with elution buffers of high salt concentration, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention commensurate with the scope of the claims.

Prior art made of record:

The following prior art is made of record and not relied upon is considered pertinent to applicant's disclosure. Belford et al. (1997, J of Endocrinology 154:45-55) discloses isolation of a fraction rich in growth factors, including TGF-β and IGF-1, from whey by single step cation exchange chromatography. Kussendrager et al. (1998 EP 0869134) teaches a process for recovering one or more growth factors from milk or milk derivatives comprising adsorbing the starting product to a cation exchanger, followed by fractionated elution of the cation exchanger. Quinque et al. (1992, WO 9200014) teach

a two step method to isolate growth factors from colostrums, the method comprising contacting the colostrums with a cation exchanger and subjecting the fraction obtained by elution of the cation exchanger to hydroxyapatite adsorption. The fraction retained on the hydroxyapatite is recovered by elution with phosphate buffer. The retained, active fraction contains growth factors. However, none of these teachings, either individually or combined, anticipate the methods of the claimed invention: a two step process to obtain fractions specifically enriched for IGF-1, specifically enriched for TGF-β, and specifically enriched for lactoperoxidase.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS

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